**Title:** Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol

**Running Head:** Treatment options for hormone-naïve prostate cancer

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# ABSTRACT


## Background

Adding abiraterone acetate with prednisolone (AAP) or docetaxel with prednisolone (DocP) to standard-of-care (SOC) each improved survival in STAMPEDE: a multi-arm multi-stage platform randomised controlled protocol recruiting patients with high-risk locally advanced or metastatic PCa starting long-term androgen deprivation therapy (ADT). The protocol provides the only direct, randomised comparative data of SOC+AAP vs SOC+DocP.

## Method

Recruitment to SOC+DocP and SOC+AAP overlapped Nov-2011—Mar-2013. SOC was long-term ADT or, for most non-metastatic cases, ADT for ≥2yrs and RT to the primary tumour. Stratified randomisation allocated pts 2:1:2 to SOC; SOC+docetaxel 75mg/m$^2$ 3-weekly x6 + prednisolone 10mg daily; or SOC+abiraterone acetate 1000mg + prednisolone 5mg daily. AAP duration depended on stage & intent to give radical RT. The primary outcome measure was death from any cause. Analyses used Cox proportional hazards & flexible parametric models, adjusted for stratification factors. This was not a formally-powered comparison. A hazard ratio (HR)<1 favours SOC+AAP, HR>1 favours SOC+DocP.

## Results

566 consenting patients were contemporaneously randomised: 189 SOC+DocP, 377 SOC+AAP. The patients, balanced by allocated treatment were: 342 (60%) M1; 429 (76%) Gleason 8-10; 449 (79%) WHO performance status 0; median age 66yr & median PSA 56ng/ml. With median follow-up 4 years, 149 deaths were reported. For overall survival, HR=1·16 (95%CI 0·82-1·65); failure-free survival HR=0·51 (95%CI 0·39-0·67); progression-free survival HR=0·65 (95%CI 0·48-0·88); metastasis-free survival HR=0·77 (95%CI 0·57-1·03); prostate cancer-specific survival HR=1·02 (0·70-1·49); and symptomatic skeletal events HR=0·83 (95%CI 0·55-1·25). In the safety population, the

proportion reporting ≥1 grade 3, 4 or 5 adverse events ever was 36%, 13% and 1% SOC+DocP, & 40%, 7% and 1% SOC+AAP; prevalence 11% at 1 and 2yrs on both arms. Relapse treatment patterns varied by arm.

**Conclusions**

This direct, randomised comparative analysis of two new treatment standards for hormone-naïve prostate cancer (HNPC) showed no evidence of a difference in overall or prostate cancer-specific survival, nor in other important outcomes such as symptomatic skeletal events, suggesting that Worst toxicity grade over entire time on trial was similar but comprised different toxicities in line with the known properties of the drugs.

**Trial registration**

Clinicaltrials.gov: NCT00268476

# RESEARCH IN CONTEXT

### Evidence before this study

Abiraterone acetate plus prednisone/prednisolone (AAP) and docetaxel with prednisone/prednisolone (DocP) have separately been shown to improve survival when used in addition to the previous international standard-of-care for hormone-sensitive prostate cancer of androgen deprivation therapy with further therapy such as AAP or DocP on relapse. This has been confirmed in a number of separate trials and on meta-analysis. The largest body of evidence for both AAP and DocP comes from the STAMPEDE platform trial.

### Added value of this study

Recruitment to DocP and AAP overlapped in STAMPEDE giving the only head-to-head evidence comparing these two new standard treatment approaches. We report data from the 566 patients who were directly randomised between these two treatment approaches while the two research arms were both open to recruitment. The data show strong evidence favouring SOC+AAP on earlier, more biochemically driven outcome measures. For longer-term, more clinically-driven outcome measures, including bone complications, prostate cancer-specific and overall survival, there is no evidence of a significant difference between AAP and DocP.

### Implications of all the available evidence

The reported trials and meta-analyses showed a larger effect on survival for AAP over the previous standard-of-care than did DocP over the standard standard-of-care. These data show that the story may be more complicated. No other directly randomised data on survival of these treatments are available. Individual patient data network meta-analysis using all of the published trials are warranted, accounting for differences in patient characteristics, treating clinicians and centres and salvage treatment access. The STAMPEDE team is collaborating with the STOPCAP meta-analysis group to achieve this.

# 1. INTRODUCTION

For several decades, the standard-of-care (SOC) for most patients with high-risk locally advanced or metastatic prostate cancer has been long-term androgen deprivation therapy (ADT) alone. The past few years there have been great changes, first with results from randomised controlled trials showing a survival advantage compared to ADT alone for adding radiotherapy to the prostate in men with non-metastatic disease and no known nodal involvement;[1-3] then with systemic treatments for all men starting long-term hormone therapy: docetaxel plus prednisolone/prednisone (DocP)[4-9] and, most recently, abiraterone acetate plus prednisolone/prednisone (AAP).[10,11] As both therapeutic combinations are effective, there are now two distinct standards-of-care with little information to guide clinicians as to which is the more effective; there are no prospective, powered, randomised controlled trials that will deliver direct comparative data.

STAMPEDE is a multi-arm, multi-stage platform protocol which assessed both of these treatment approaches, separately, against the previous SOC.[12,13] The "docetaxel comparison" of STAMPEDE recruited patients allocated to SOC+DocP between Oct-2005 and Mar-2013. The "abiraterone comparison", the first comparison to be added to STAMPEDE, recruited patients allocated to SOC or SOC+AAP between Nov-2011 and Jan-2014. Each of those comparisons had primary outcome measure of overall survival for the patients randomised contemporaneously to the control arm and the relevant research arm. Consequently between 15-Nov-2011 and 31-Mar-2013, patients were directly randomised contemporaneously between these two research arms (and other research arms) and we now present these data.

# 2. METHODS

## 2.1 Trial design

The STAMPEDE protocol and design have been described in detail elsewhere.[7,10,12,14] Briefly, STAMPEDE comprises a series of multi-arm multi-stage comparisons that have overlapped in recruitment and follow-up time.

## 2.2 Patient selection

Eligible patients were those starting long-term ADT for the first time. This was defined as patients with metastatic disease, nodal involvement or node negative, non-metastatic disease with two or more of three high-risk features: T-category 3 or 4, Gleason sum score 8-10 or PSA>40ng/ml. Patients rapidly relapsing after previous local therapy were also permitted if they had PSA>20ng/ml or PSA>4ng/ml with a PSA doubling time <6 months or those who developed loco-regional or metastatic spread whilst not on hormone therapy.

As with all STAMPEDE comparisons, the primary outcome measure of the two underpinning comparisons (against control) was overall survival. Failure-free survival was an intermediate primary outcome measure, defined as time from randomisation to the first of: rising PSA (where rising PSA was defined as a confirmed rise to >4ng/ml, and >50% above the lowest value in the first 6 months after randomisation); new disease or progression of: distant metastases, lymph nodes or local disease; or death from prostate cancer. Progression-free survival was defined as time from randomisation to the first of: new disease or progression of: distant metastases, lymph nodes or local disease; or death from prostate cancer.[15] Metastatic progression-free survival (MPFS) was defined as time from randomisation to death from any cause, new metastases or progression of distant metastases.

All patients provided written informed consent; all versions of the protocol have been reviewed by the relevant research ethics committees and the regulatory agencies; the original

protocol and all subsequent versions involving the introduction of a new research arm and comparison were independently peer-reviewed by Cancer Research UK.

Patients have been allocated across a number of research treatments as depicted in **Figure_1**. Here we focus on those patients randomised between 15-Nov-2011 and 31-Mar-2013, while both the "docetaxel comparison" and the "abiraterone comparison" were open to recruitment, and who were allocated to either SOC+DocP or SOC+AAP.

## 2.3 Trial treatment, masking and follow-up

The standard-of-care was long-term hormone therapy with LHRH analogues (with short term anti-androgen if relevant) or orchidectomy. Unless contraindicated, radiotherapy to the prostate was mandated in all patients with N0M0 disease, encouraged in patient with N+M0 disease, and permitted in patients with M1 disease until the activation of the "M1|RT comparison" in Jan-2013. On the DocP arm, docetaxel (75mg/$m^2$) was given once every three weeks for six cycles, with prednisolone/prednisone (10mg) daily. On the AAP arm, abiraterone acetate (1000mg) with prednisolone/prednisone (5mg) daily was given until PSA, clinical and radiological progression or a change of treatment. AAP duration was capped after 2 years in M0 patients having radical radiotherapy. Modifications for toxicities were described in the protocol and previous papers.[7 10] Treatment allocation was not masked for practical reasons. Patients were seen 6-weekly at first, dropping to 6-monthly after 2 years. Imaging scans after baseline were at the investigator's discretion.

## 2.4 Randomisation

Patients were randomised centrally using minimisation with a random element across a number of stratification factors using unequal allocation (previously described).[7,10] The allocation ratio was initially 2:1 control:research; the "abiraterone comparison" was brought in with an equal allocation (1:1) ratio to the control. Therefore the allocation ratio here is 1:2 for SOC+DocP:SOC+AAP.

## 2.5 Statistical analysis

The comparison presented here is of SOC+AAP against SOC+DocP because both of these arms have demonstrated better overall survival than their contemporaneous controls in the population of men starting long-term hormone therapy. The protocol specified that research arms which were better than the control arm could be compared, following a closed test approach. The maturity of the data used for SOC+AAP matches that recently reported[10] in the primary results and is updated to the same data freeze timepoint for SOC+DocP so is longer-term data than previously reported results for this arm.[7]

The previously-reported comparisons of SOC+DocP vs SOC and SOC+AAP vs SOC had formal sample size calculations; there is no formal sample size calculation for this comparison: it is an opportunistic comparison between the contemporaneously-recruited research arm patients. Although the recruitment overlap is only 17 months, 566 patients were allocated to the two research arms of interest and thus contribute substantial information to inform this comparison.

Standard survival analysis methods were used, following the approach for each of these underpinning comparisons; hazard ratios (HR) were estimated from adjusted Cox models, after checking that the proportional hazards assumption held, where a hazard ratio (HR)<1 represents evidence in favour of SOC+AAP and HR>1 represents evidence in favour of SOC+DocP. Nominal confidence intervals are presented at the 95% level. A p-value <0.1 was considered indicative of treatment-baseline characteristic interaction, recognising the limited power of the heterogeneity tests. Efficacy analyses were done in the intention-to-treatment basis, by allocated treatment. Safety analyses were done only in patients who started their allocated treatment.

## 2.6 Role of the funding source

The trial was sponsored by the UK Medical Research Council (MRC) and conducted by the MRC Clinical Trials Unit at UCL. In the United Kingdom the trial was supported by the UK Clinical Research Network, and funded by Cancer Research UK and the Medical Research Council, and in Switzerland, by the Swiss Group for Cancer Clinical Research (SAKK). Industry collaboration and support has been provided to STAMPEDE by Astellas, Clovis Oncology, Janssen, Novartis, Pfizer and Sanofi-Genzyme. MRC employees were central to the conduct of the trial and the development of this manuscript. Authors MRSy and MRSp accessed raw data. The funding bodies had no role in determining this publication.

# 3. RESULTS

## 3.1 Accrual and characteristics

The dataset for this comparison was frozen on 10-Feb-2017. Between 15-Nov-2011 and 31-Mar-2013, 1,348 patients joined all open arms STAMPEDE. Of the 566 randomised to the comparison reported here, 189 (14%) were allocated to SOC+DocP, 377 (28%) to SOC+AAP. The flow of patients to this comparison is shown in **Figure_2**. **Table_1** shows the baseline characteristics of patients in this comparison which differ only slightly from the previous papers (summarised in **Supp_Table_1)** Median follow-up, calculated by reverse censoring on survival, was 48 months.

## 3.2 Overall survival

There were 44/189 (23%) deaths on the SOC+DocP arm and 105/377 (28%) deaths on the SOC+AAP arm. The estimated HR=1·16 (95%CI 0·82-1·65; p=0·40) (**Figure_3A**). Estimates in patients with and without metastases are shown in **Table_2**, with HR=1·51 (95%CI 0·58-3·93) in M0 patients and HR=1·13 (95%CI 0·77-1·66) in M1 patients. There was no evidence of interaction in the treatment effect by baseline metastases (p=0·69).

126/149 deaths were attributed to prostate cancer, comprising 10/22 and 116/127 deaths in patients with M0 and M1 disease at entry, respectively. Competing risks regression shows no evidence of a difference in prostate cancer-specific survival (sub-HR=1·02, 95%CI 0·70—1·49). For non-prostate cancer-specific survival, with 23/149 deaths attributed to other causes, the sub-HR was 2·33 (95%CI 0·78-6·99). There was no evidence of heterogeneity of treatment effect by baseline metastases in either outcome.

## 3.3 Other efficacy outcome measures

**Table_2** shows the effect size overall and by whether the patients had metastases at entry for failure-free survival, progression-free survival, metastatic progression-free survival and

skeletal related events. There is no evidence of heterogeneity of the treatment effect by baseline metastases in any of these outcome measures. **Figure_4** summarises the effect for all outcome measures.

### 3.4 Safety

The safety population includes people who started their allocated treatment. While nearly all patients allocated to AAP started it, a proportion of those patients allocated to receive docetaxel declined to start it. **Table_3** summarises the worst toxicity reported for patients over their time on trial in the safety population and shows differing patterns for adverse events according to treatment. The prevalence of grade 3 or 4 toxicity in patients with assessments at 1 year without a prior FFS event was 11% SOC+DocP and 11% SOC+AAP; at 2 years this was 11% SOC+DocP and 11% SOC+AAP.

### 3.5 Second-line treatment

**Figure_5** shows time from randomisation to any subsequent exposure to docetaxel or AR-targeted therapy with AAP or enzalutamide. **Figure_6** shows time from an FFS event to reported exposure to selected treatments that are licensed for CRPC: docetaxel, AAP, enzalutamide. There was limited reported use of cabazitaxel, radium and sipuleucel-T at this point (not shown).

# 4. DISCUSSION

We and others have previously shown a survival advantage for adding docetaxel (with or without prednisolone/prednisone) and for adding abiraterone acetate and prednisolone/prednisone, in patients starting long-term hormone therapy for the first time.[4-11] However, there is currently no direct evidence available to help clinicians or patients assess which combination might be better. Here, we reported a pre-specified (but not pre-powered) analysis using only patients who were randomised during a period of the study when recruitment to the two research arms overlapped. We used data collected prospectively from over 100 sites across two countries as part of a clinical trial protocol. The MAMS platform design of STAMPEDE, an approach sometimes referred to as a master protocol,[16] facilitated this comparison. Separate, traditional, two-arm RCTs, would not have allowed any directly-randomised comparative evidence to be available so soon.

Our recently-reported overall treatment effect on survival, in STAMPEDE, for adding AAP compared to the standard-of-care (HR=0·63)[10] was larger than the previously-reported overall treatment effect, in STAMPEDE, on survival for adding DocP to the same standard-of-care (HR=0·78).[7] The earlier secondary efficacy outcome measures favoured adding AAP over DocP, including failure-free survival -- perhaps unsurprising given the direct anti-androgenic action of AAP (around four in every five FFS events was driven only by a rise in PSA) and progression-free survival (which excludes rising PSA). There was weak evidence favouring AAP for metastatic progression-free survival and no evidence of a difference in symptomatic skeletal events, prostate cancer-specific survival or overall survival.

Comparing the results indirectly of these two therapies by readers extracting data from STAMPEDE's AAP and docetaxel papers[7,10] may not be the most appropriate way to compare the relative effectiveness: the patient cohorts were all not randomised contemporaneously and there may be confounding biases when comparing the two datasets, in particular, many

DocP patients had very limited salvage CRPC options compared to AAP patients, simply due to the timing of licences of new therapies (see below).

Importantly, the two therapies are being used in different ways. AAP is used until the patient has castrate-resistant prostate cancer (CRPC), often lasting many years and consequently exhausting a major therapy option for CRPC. In contrast, DocP is given as an 18 week course thus all CRPC options should remain available. Our data reveal important differences in the pattern of treatment failure yet we do not see any differences in survival, suggesting that the relative time spent before and after first-line treatment failure are quite different by initial treatment. This may explain why the early, often biochemically-driven outcome measures, favour AAP but the later post CRPC endpoints such as skeletal events, prostate cancer-specific survival and overall survival show no good evidence of a difference. Men receiving DocP will thus spend longer with CRPC than men receiving AAP but with a broader range of more effective options available. **Supp_Figure_1** shows the status of all patients at each moment in time after randomisation. That the DocP cohort had more durable survival after failure, perhaps longer than before failure, may be important in counselling patients biochemically failing after DocP.

The number of events is an important consideration in time-to-event analyses. The number of patients with metastases at baseline was balanced by arm, but, particularly because of their poorer prognosis, these patients tend to predominate in this analysis. There is no evidence of heterogeneity in the treatment effect by baseline metastasis for any of the outcome measures, but power to detect any heterogeneity is very limited, especially in later outcome measures with fewer events.

The patterns of toxicity are quite different for the two treatment approaches, consistent with the known effects of the drugs. The proportion of patients reporting at least one grade 3 or worse toxicity was similar and in line with previously reported toxicities for these agents

(**Table_3**). In patients who started their allocated treatment and who are without disease progression at 1 year, the prevalence of grade 3 or worse toxicity was about 11% on both arms and very similar to our previous estimate for SOC. Nearly all patients started their allocated abiraterone, whereas about one in twelve patients did not start their allocated docetaxel. Our results may change future compliance with both treatments in routine practice; but the lack of compliance with allocated treatment for docetaxel is likely to have had some impact on our estimated effect sizes.

A key limitation is that the comparison was opportunistic and not designed in the usual way, hence power is limited to detect any realistic differences. The trigger for the analysis was the reporting of our "abiraterone comparison" data.[10] The unequal allocation ratio reflects the planned design of the comparisons. The allocated treatment being given was not masked for practical reasons. This, of course, allowed for relapse therapies to be given at the investigator's discretion. We observed that after relapse, many patients received the treatment class that they had not received up-front.

Salvage options have changed over time: men recruited earlier on to DocP (2005-2013) will have had very different options to those recruited later to AAP (2011-2014) when there were more CRPC therapies likely available, including AAP,[17,18] cabazitaxel,[19] docetaxel,[20,21] enzalutamide,[22,23] radium-223[24] and sipuleucel-T[25] (although not widely accessible in Europe). For this analysis, we limited ourselves to patients contemporaneously randomised to either arm to make this comparison as fair as possible. However, failure-free survival events generally happened sooner with DocP than with AAP in time from randomisation and, therefore, calendar year (**Table_4)** may partially influence outcomes. Furthermore, a FFS event was more of an indication to change treatments on DocP; AAP continued beyond this point.

As far as we are aware there are no ongoing randomised trials directly comparing adding AAP vs adding docetaxel for patients starting long-term ADT. All of our published STAMPEDE data have contributed to the STOpCaP aggregate data network meta-analysis which has used all of the reported randomised controlled trials in metastatic patients to perform indirect comparisons and allow some assessment of potential ranking of effective therapies. This aggregate data analysis (**co-submitted**) will be supplemented by a forthcoming individual patient data (IPD) network meta-analysis which will hopefully provide a more accurate reflection of the temporal interval between the application of the two different therapies, to which STAMPEDE will contribute all relevant data. We will continue to follow-up patients for long-term outcome measures.

Considering their mechanisms of action and their proven oncological benefits, the question is raised of whether a combination of AAP plus docetaxel might lead to an approximately additive benefit of using them both, further extending survival. Randomised data on docetaxel with or without abiraterone will emerge from a subset the PEACE-1 trial[a], as will non-randomised, time-stratified data on abiraterone with or without docetaxel. Similarly comparative data will also emerge for enzalutamide, another AR-targeted therapy, from the ENZAMET trial[b] and with the combination of enzalutamide and AAP in STAMPEDE (**Figure 1**).

[a] https://clinicaltrials.gov/ct2/show/NCT01957436
[b] https://clinicaltrials.gov/ct2/show/NCT02446405

In conclusion, there are now two systemic therapies, DocP and AAP, which have shown a survival benefit from randomised controlled trials when added to treatment for patients starting long-term androgen deprivation therapy for the first time. The evidence from our directly randomised data comparing these two therapies showed no evidence of a difference in overall or prostate cancer-specific survival, nor in other important outcomes such as symptomatic skeletal events, suggesting that both currently remain viable new standards-of-care.

# ABBREVIATION LIST

| Abbreviation | Expansion |
|---|---|
| AAP | Abiraterone acetate and prednisolone (UK) / prednisolone (Switzerland) |
| ADT | Androgen deprivation therapy |
| CRPC | Castrate-resistant prostate cancer |
| CRUK | Cancer Research UK |
| CTA | Clinical Trials Authorisation |
| CTU | MRC Clinical Trials Unit |
| DocP | Docetaxel and prednisolone |
| FFS | Failure-free survival |
| HNPC | Hormone-naïve prostate cancer |
| HR | Hazard ratio |
| IDMC | Independent Data Monitoring Committee |
| IQR | Interquartile range |
| MAMS | Multi-arm Multi-stage |
| MRC | Medical Research Council |
| MPFS | Metastatic progression-free survival |
| MRC | Medical Research Council |
| OM | Outcome measure |
| OS | Overall survival |
| PFS | Progression-free survival |
| PIS | Patient Information Sheet |
| RCT | Randomised Controlled Trial |
| SOC | Standard-of-care |
| STAMPEDE | Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UCL | University College London |
| WHO PS | WHO performance Status |

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Grant holders -- MRSy, MKBP, NDJ, MDM, DPD, NWC

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TMG vice chairs – MDM, NWC

TMG members -- MKBP, MRSy, DPD, NC, BC, SG, ZM, SC, CCP, GA, DM, JMR, RJ

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Analysis plan -- MRSy, MRSp, MKBP, NJ

Performed analyses – MRSy, MRSp

Interpreted data – [All]

Wrote critical sections of manuscript – MRSy, MRSp, NDJ, MKBP, MDM, NWC

Edited and approved final manuscript – [All]

Reviewed and approved final manuscript – [All]

## COMPETING INTERESTS

See separate forms

# ACKNOWLEDGEMENTS


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**Independent Data Monitoring Committee:** John Yarnold (chair), Doug Altman, Ronald de Wit, Bertrand Tombal; *Previous* --- Reg Hall, Chris Williams

**Trial Steering Committee:** Jonathan Ledermann (chair), Jan Erik Damber, Richard Emsley, Alan Horwich; *Previous* --- John Fitzpatrick, David Kirk, Jim Paul

### PARTICIPATING SITE LIST

**Structure: City, Hospital** (Number of patients by data freeze: site PI; other investigators)

**United Kingdom**

- **Aberystwyth, Bronglais General Hospital** (4: Porfiri; Durrani)
- **Ashford William Harvey Hospital** (19: Thomas; Mithal)
- **Aylesbury, Stoke Mandeville Hospital** (14: Sabharwal; Camilleri)
- **Ayr Hospital** (54: Glen; Ansari)
- **Barnet General Hospital** (25: McGovern; Eichholz)
- **Basingstoke & N Hampshire Hospital** (21: Shaffer)
- **Bath, Royal united Hospital** (70: Frim; Beresford)
- **Belfast City** (191: O'Sullivan; Mitchell, Stewart, Shum)
- **Birmingham, City Hospital** (26: Sivoglo; Ford)
- **Birmingham, Good Hope Hospital** (18: Ford)
- **Birmingham, Heartlands Hospital** (38: Zarkar)
- **Birmingham, QE** (180: James; Porfiri, Ford)
- **Blackburn East Lancashire Trust** (180: Parikh; Charnley)
- **Bolton, Royal Bolton Hospital** (30: Elliott, Maddineni)
- **Boston, Pilgrim Hospital** (38: Sreenivasan; Panades)
- **Bournemouth, Royal Bournemouth Hospital** (100: Brock)
- **Bradford Royal Infirmary** (36: Brown)
- **Brighton, Royal Sussex County Hospital** (92: Robinson; Robinson, Bloomfield)
- **Bristol H & O Centre** (106: Bahl; Herbert, Masson)
- **Burton, Queen's Hospital** (108: Smith-Howell; Chetiyawardana, Pattu)
- **Bury St Edmunds, West Suffolk Hospital** (21: Woodward)
- **Cardiff, Velindre** (341: Lester; Staffurth, Barber, Kumar, Palaniappan, Button, Tanguay)
- **Chelmsford, Broomfield Hospital** (88: Hamid; Panwar, Leone)
- **Cheltenham General Hospital** (54: Bowen)
- **Chester, Countess of Chester Hospital** (79: Ibrahim)
- **Coventry & Warwickshire, University Hospital** (40: Worlding; Stockdale)
- **Crewe, Leighton Hospital** (54: Wylie)
- **Cumbria, Cumberland Infirmary** (18: Kumar)
- **Darlington Memorial Hospital** (49: Kagzi; Hardman, Peedell)
- **Derby, Royal Derby Hospital** (130: Chakraborti; Pattu)
- **Devon, North Devon District Hospital** (33: Sheehan)
- **Doncaster Royal Infirmary** (35: Bowen; Ferguson)
- **Dorset County Hospital** (30: Crellin; Afzal, Andrews)
- **Dudley, Russells Hall Hospital** (81: Keng-Koh; Ramachandra)
- **Durham University Hospital** (17: Heath; McMenemin)
- **Eastbourne District General Hospital** (63: McKinna)

- **Edinburgh, Western General** (112: McLaren)
- **Essex County Hospital** (58: Muthukumar; Sizer, Kumar)
- **Exeter, RD&E** (189: Sheehan; Srinivasan)
- **Gillingham, Medway Hospital** (29: Kumar; Taylor)
- **Glasgow, BOC** (323: Graham; Venugopal, Wallace, Jones, Lamb, Glen, Russell)
- **Guildford, Royal Surrey County Hospital** (132: Laing; Khaksar, Wood, Money-Kyrle)
- **Harlow, Princess Alexandra Hospital** (54: Gupta; Melcher, Melcher)
- **Hereford County Hospital** (71: Grant; Cook)
- **Huddersfield Royal Infirmary** (105: Hofmann)
- **Hull, Castle Hill Hospital** (119: Simms; Hetherington)
- **Inverness, Raigmore Hospital** (88: McPhail; MacGregor)
- **Ipswich Hospital** (103: Brierly; Venkitaraman, Scrase)
- **Keighley, Airedale Hospital** (52: Brown; Crawford)
- **Kent and Canterbury Hospital** (79: Thomas; Raman, Mithal, Malde)
- **Kent, QE Q Mother Hospital** (27: Thomas; Raman)
- **Kidderminster General Hospital** (40: Capaldi; Churn)
- **Larbert, Forth Valley Royal Hospital** (36: Sidek)
- **Leeds, St James University Hospital** (94: Cross; Loughrey, Bottomley, Prescott)
- **Lincoln County Hospital** (50: Sreenivasan; Ballesteros-Quintail, Panades, Baria)
- **Liverpool, Royal Liv University Hospital** (88: Malik; Robson, Eswar)
- **Liverpool, UH Aintree** (26: Robson)
- **London, Charing Cross Hospital** (38: Falconer; Mangar)
- **London, Guy's Hospital** (161: Chowdhury)
- **London, Hammersmith Hospital** (4: Falconer; Mangar)
- **London, N Middlesex Hospital** (24: Gupta; Newby, Thompson)
- **London, Royal Free Hospital** (44: Vilarino-Varela; Pigott)
- **London, St Georges Hospital** (35: Pickering)
- **London, St Mary's Hospital** (8: Falconer; Stewart)
- **London, UCH** (46: McGovern)
- **Maidstone, Kent Oncology Centre** (114: Beesley)
- **Manchester Christie Hospital** (167: Clarke; Elliott, Livsey, Choudhury, Wylie)
- **Manchester Hope Hospital** (59: Clarke; Elliott, Lau, Tran)
- **Manchester, Royal Oldham Hospital** (54: Conroy; Livsey, Choudhury)
- **Manchester, Withington Hospital** (7: Sangar)
- **Middlesbrough, James Cook UH** (103: Peedell; Van der Voet, Hardman, Shakespeare)
- **Newcastle, Freeman Hospital** (92: Azzabi; McMenemin, Frew)
- **North Staffordshire UH** (80: Adab)
- **Northwood, Mount Vernon Hospital** (126: Hoskin; Anyamene, Ostler, Alonzi)
- **Nottingham University Hospitals** (City Campus) (141: Sundar; Mills)
- **Nuneaton, George Eliot Hospital** (14: Khan; Chan)
- **Oxford, Churchill Hospital** (165: Protheroe; Cole, Sabharwal, Sugden)
- **Poole Hospital** (62: Davies)
- **Portsmouth, Q Alexandra Hospital** (173: Gale)
- **Preston, Royal Preston Hospital** (221: Birtle; Parikh, Wise)
- **Reading, Royal Berkshire Hospital** (42: Rogers; O'Donnell, Brown, Brown)
- **Redditch, Alexandra Hospital** (15: Capaldi; Hamilton)
- **Romford, Queen's Hospital** (127: Gibbs; Subramaniam)
- **Scarborough General Hospital** (82: Hingorani)
- **Sheffield, Weston Park** (142: Ferguson)
- **Shrewsbury, Royal Shrewsbury Hospital** (192: Srihari)
- **Somerset, Weston General Hospital** (18: Hilman)
- **Southampton General Hospital** (75: Jones; Heath, Wheater, Crabb)
- **Southend University Hospital** (114: Tsang; Ahmed, Chan)

- **Southport and Formby District GH** (46: Bhalla; Sivapalasuntharam, Sivapalasuntharam)
- **St Leonards-on-Sea, Conquest Hospital** (42: McKinna; Beesley, Lees)
- **Stevenage, Lister Hospital** (35: Hughes)
- **Stockport, Stepping Hill Hospital** (106: Logue; Coyle)
- **Stockton-on-Tees, UH North Tees** (28: Leaning; Shakespeare)
- **Sunderland Royal Hospital** (45: Azzabi)
- **Sutton-in-Ashford, King's Mill Hospital** (64: Saunders)
- **Sutton-London, RMH** (162: Dearnaley; Parker, Selvadurai)
- **Swansea, Singleton** (188: Wagstaff; Phan, Phan)
- **Swindon, Great Western Hospital** (52: Khan; Cole)
- **Taunton, Musgrove Park Hospital** (137: Gray; Graham, Varughese, Plataniotis)
- **Torbay District General Hospital** (135: Lydon; Srinivasan)
- **Tyne & Wear, S Tyneside District Hospital** (6: Azzabi)
- **Warrington Hospital** (111: Syndikus; Tolan)
- **Warwick Hospital** (17: Chan; Stockdale)
- **Wigan, Royal Albert Edward Infirmary** (37: Tran)
- **Wirral, Clatterbridge Centre for Oncology** (128: Tolan; Syndikus, Ibrahim, Montazeri, Littler)
- **Wolverhampton, New Cross Hospital** (53: Gray; Sayers)
- **Woolwich, QE Hospital** (18: Hughes)
- **Worcestershire Royal Hospital** (57: Capaldi; Bowen)
- **Worthing Hospital** (90: Nikapota)
- **Wycombe Hospital** (52: Sabharwal; Protheroe, Pwint)

**Switzerland**

- **Basel Universitatsspital** (5: Rentsch)
- **Berne University Hospital** (Inselspital) (5: Thalmann)
- **Chur Kantonsspital Graubunden** (31: Strebel; Cathomas)
- **Kantonsspital St Gallen** (10: Engeler)
- **Lausanne,Centre Hospital Univ Vaudois** (7: Berthold; Jichlinski)

Plus more than 3,000 local site team staff across these hospitals.

**TRIALS UNIT STAFF** (**involved from 2011 onwards)**

**MRC Clinical Trials Unit at UCL**

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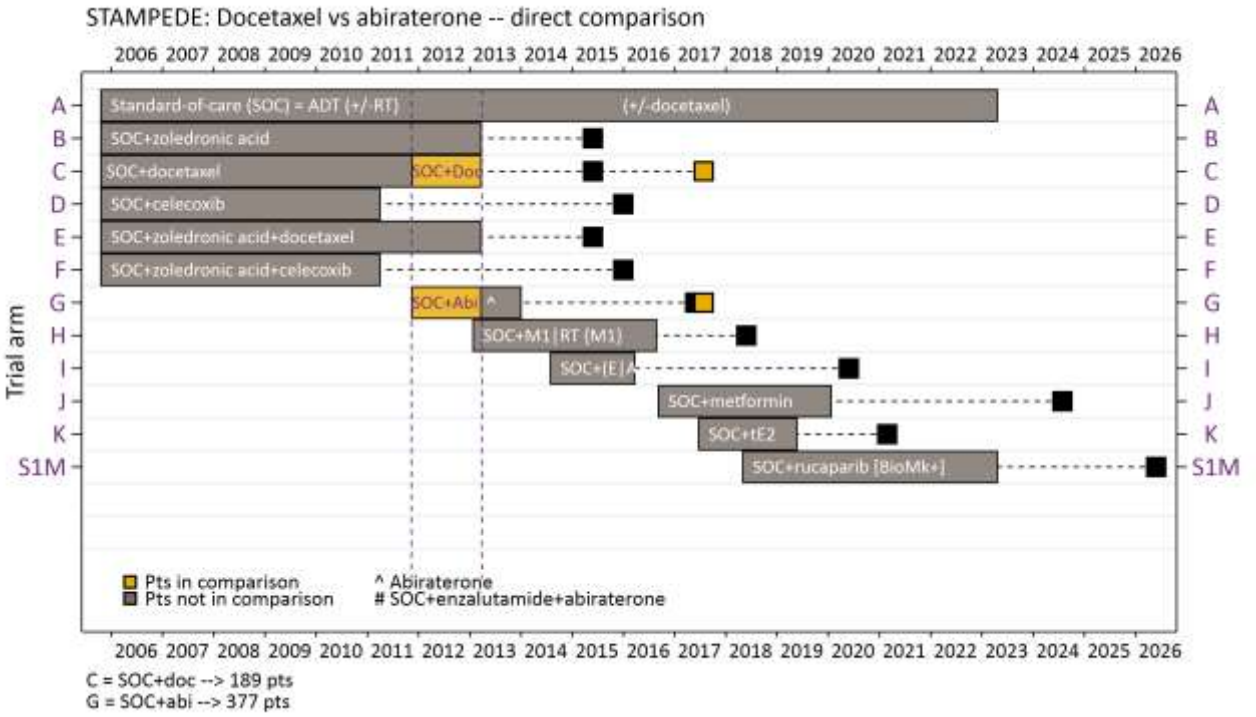
**Swiss Group for Cancer Clinical Research**

- **Project and Trial Managers** – Corinne Schar; *Previously* --- Estelle Cassolly

# TABLES AND FIGURES

**Figure 1: Activity-by-time diagram: patients included in this comparison**




**Key**

SOC = Standard-of-care

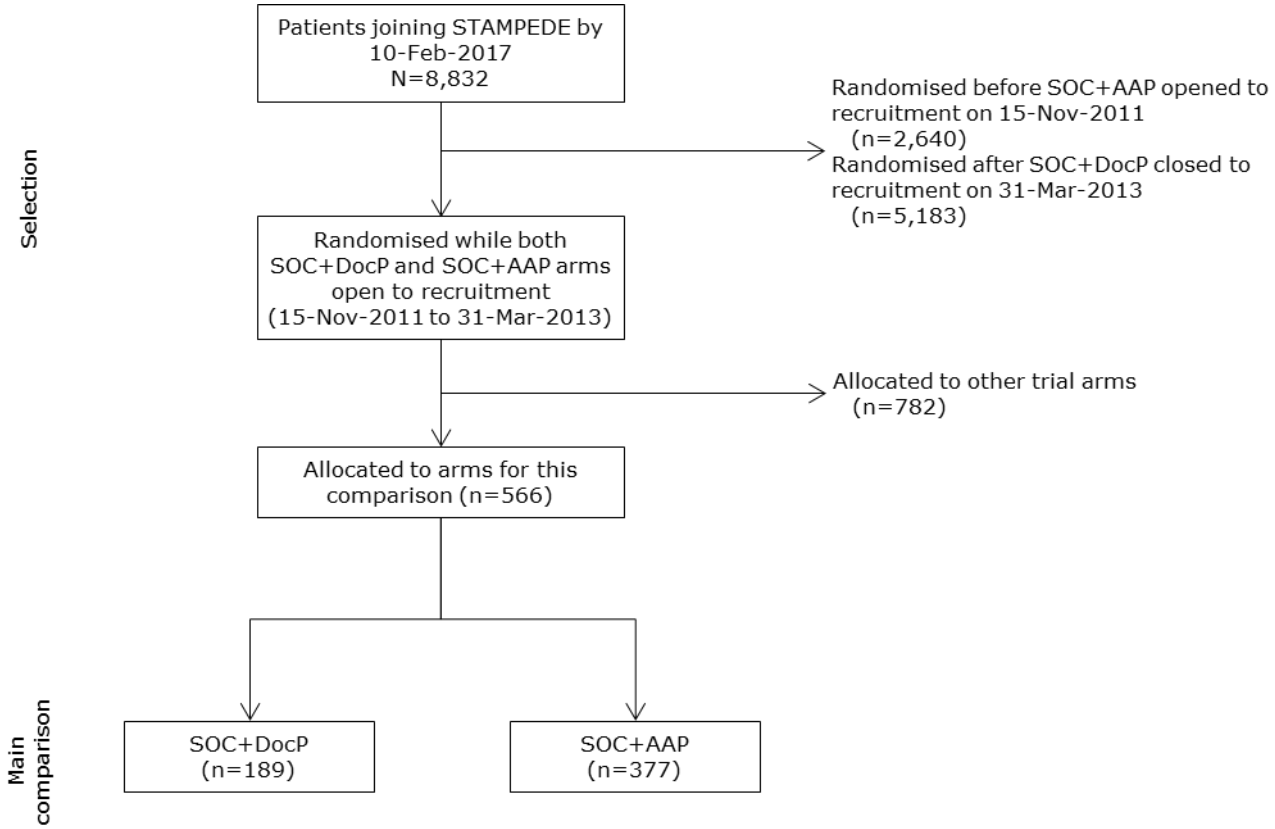
Doc = Docetaxel

Abi = Abiraterone acetate + prednisone/prednisolone

**Note**

Boxes represents periods of recruitment (x-axis) to each of the trial arms (y-axis). The yellow-bars represent recruitment periods contributing to this analysis; the grey boxes other recruitment period, past and future, contributing to other aspects of the STAMPEDE. The squares represent the time point of the first key comparative analyses for each comparison in black and for this comparison in yellow.

**Figure 2: CONSORT diagram**




**Key**

SOC = Standard-of-care

DocP = Docetaxel + prednisolone/prednisone

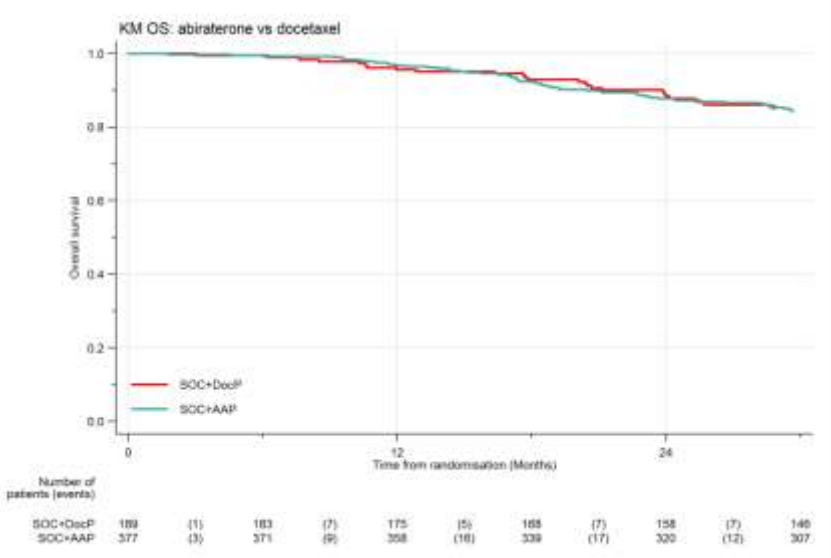
AAP = Abiraterone acetate + prednisolone/prednisone

**Note**

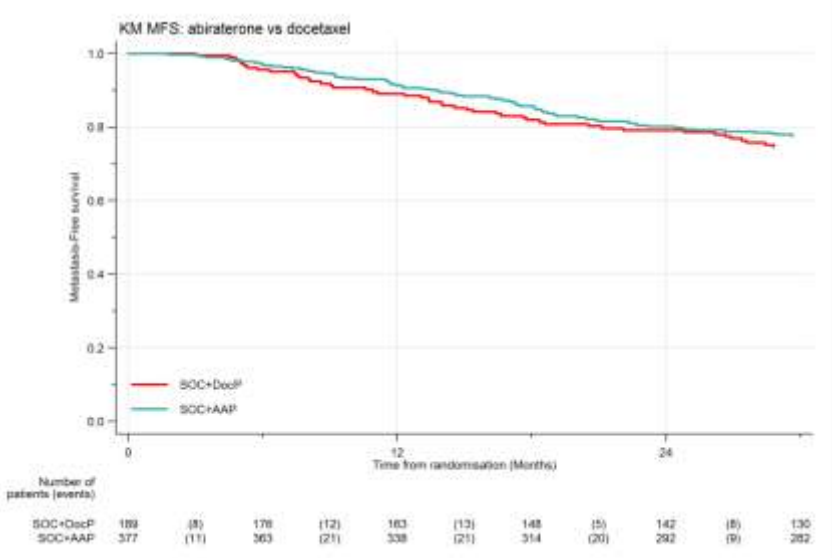
Selection of patients for this comparison

546 **Figure 3: Efficacy analysis – survival, metastases-free survival, failure-free survival, skeletal-related events**

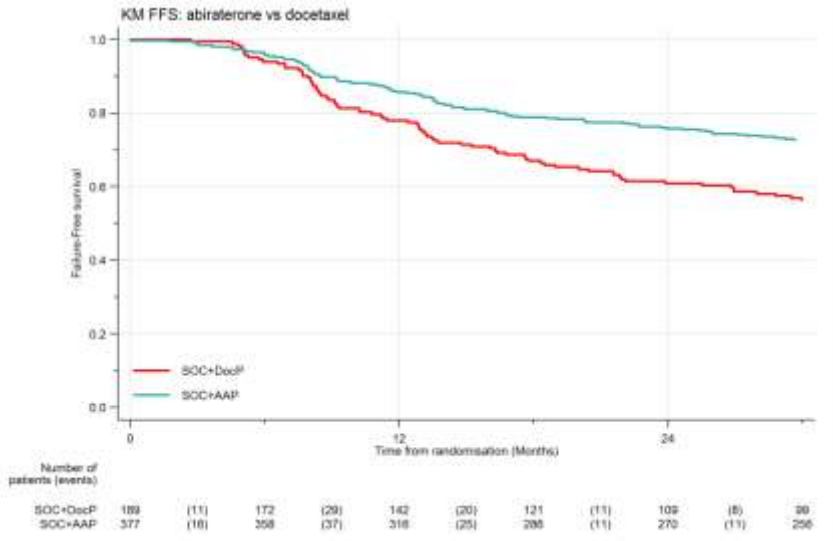
**(a) Overall survival**



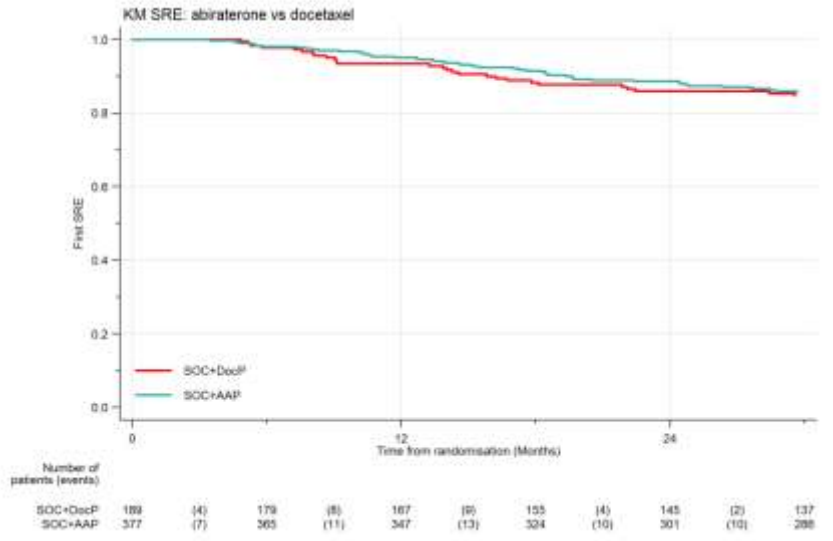

**(b) Metastases-free survival**



**(c) Failure-free survival**




**(d) Symptomatic skeletal events**

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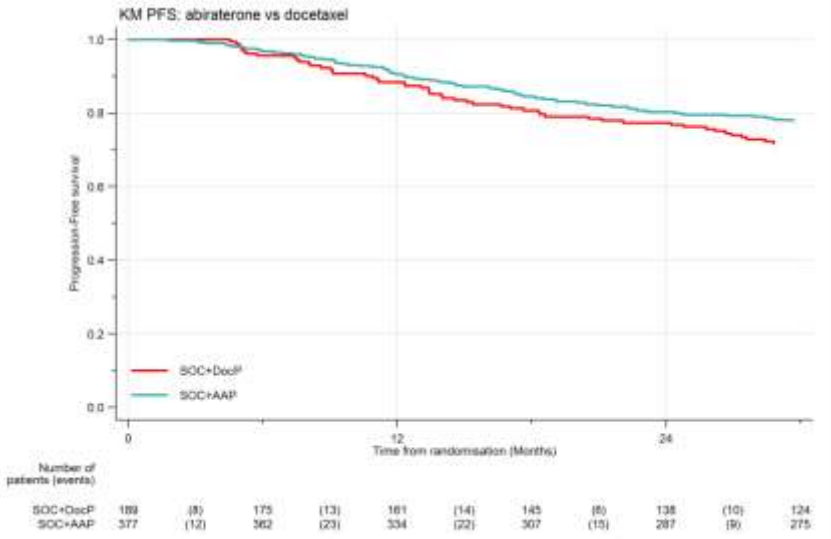
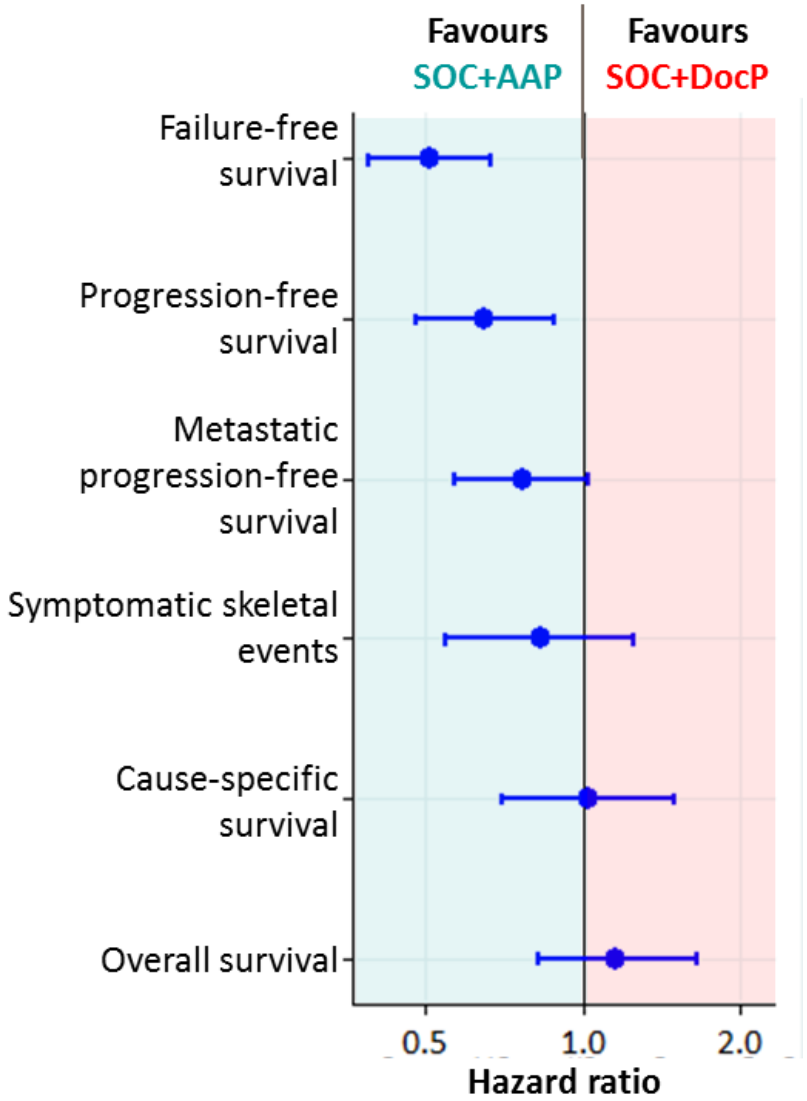
## (e) Metastatic progression-free survival




**Note**

Kaplan-Meier ("survival") plots for the key efficacy outcome measures. Each step down the y-axis represents an event. The number of patients contributing information ("at risk") over time since randomisation are shown under the table. The number of patients with an event between these points is shown in brackets. The number of patients censored in a time window is not shown, but is calculable as the difference between the number of patients at risk at two times points and the number of patients with events e.g. on Figure 3e between 0 and 6 months on the SOC+AAP arm (377-362)-12=3 patients are censored.

548 **Figure 4: Depiction of disease state over time**

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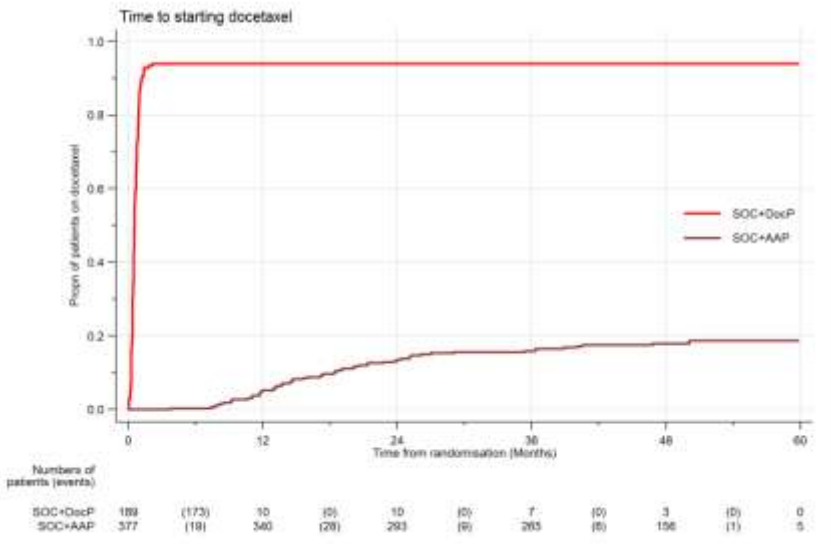
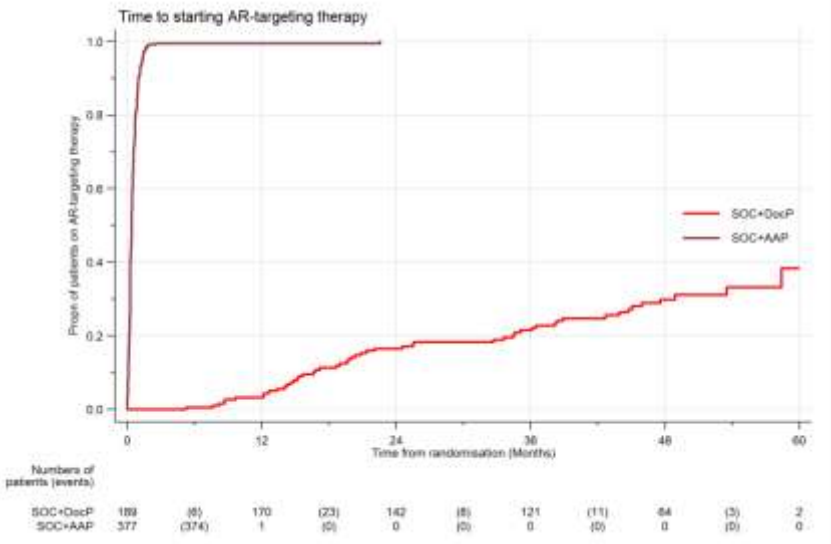
550 **Figure 5: Time from randomisation to reported starting docetaxel, AAP, enzalutamide or AR-targeting therapy**

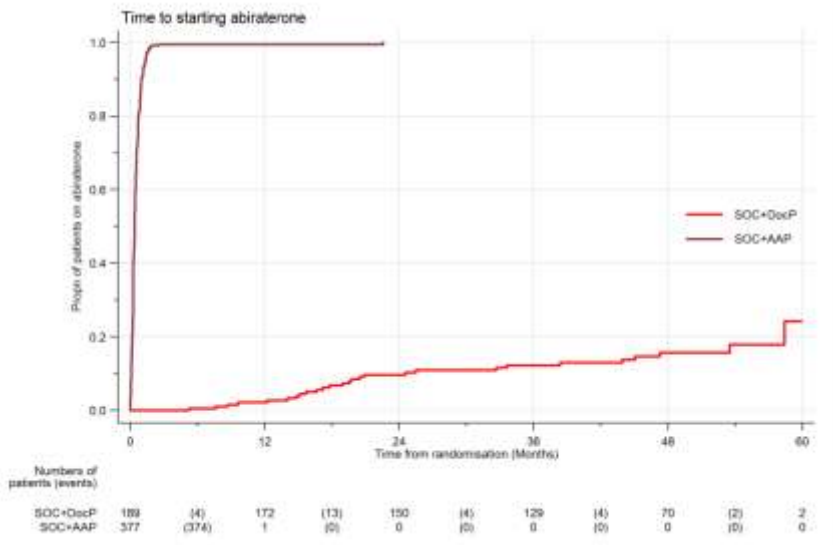
**(a) Time from randomisation to docetaxel**



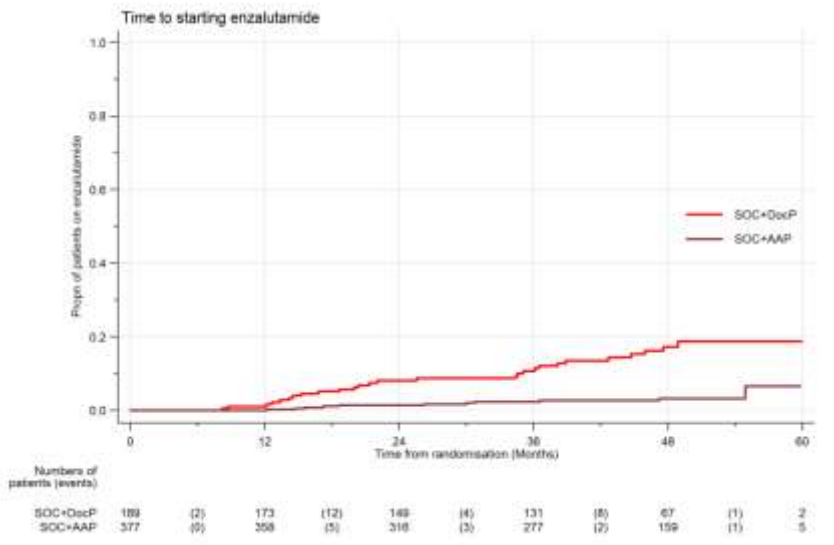

**(b) Time from randomisation to any AR-targeted therapy**



**(c) Time from randomisation to AAP**




**(d) Time from randomisation to enzalutamide**




**Note**

Kaplan-Meier ("survival") plots showing cumulative incidence of exposure to treatments after randomisation. Each step up the y-axis represents an event, namely starting that particular treatment. The number of patients contributing information ("at risk") over time since randomisation are shown under the table. The number of patients with an event between these points is shown in brackets. For example, on Figure 4c between 24 and 36 months after randomisation, 4 patients on the SOC+DocP arm report starting abiraterone and (150-129)-4 are 17 are censored and may start in the future.

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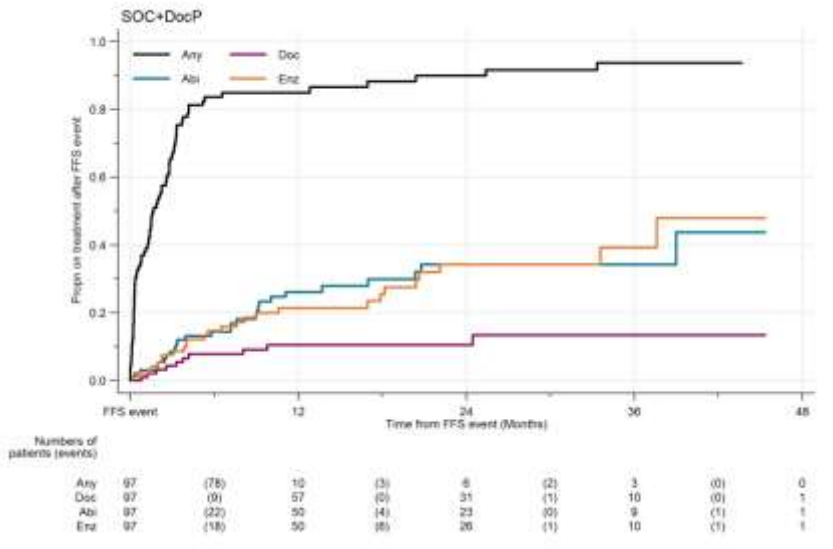
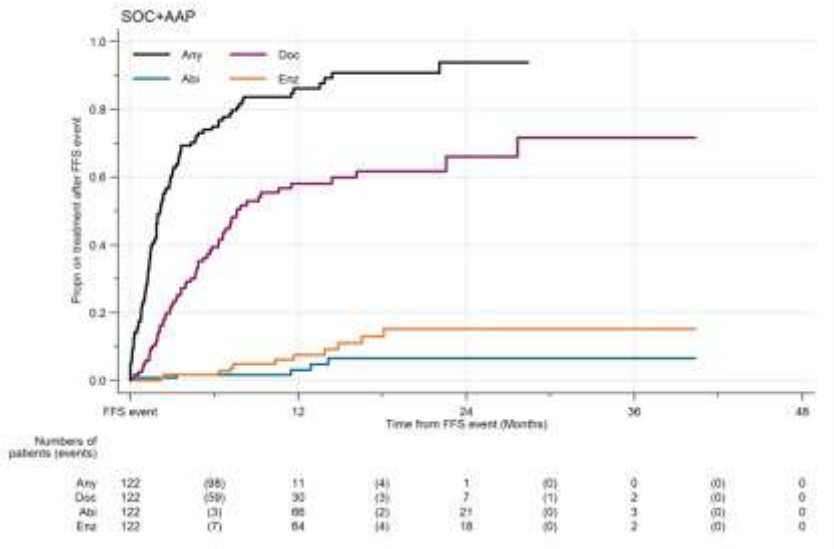
553 **Figure 6: Time from failure-free survival event to subsequent treatment by allocated treatment**

**(a) SOC+DocP allocated group**




**(b) SOC+AAP allocated group**




**Note**

Kaplan-Meier ("survival") plots showing cumulative incidence of exposure to treatments after a failure-free survival (FFS) event. Each step up the y-axis represents an event, namely starting that particular treatment.

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**Table 1: Baseline characteristics of patients allocated to SOC+DocP or SOC+AAP by whether contributing to the direct comparison**

| Characteristic | SOC+DocP | | SOC+AAP | | Overall | |
|---|---|---|---|---|---|---|
| | | | | | N | % |
| **Metastases** | | | | | | |
| M0 | 74 | 39 | 150 | 40 | 224 | 40 |
| M1 | 115 | 61 | 227 | 60 | 342 | 60 |
| **Nodal stage** | | | | | | |
| N0 | 82 | 43 | 158 | 42 | 240 | 44 |
| N+ | 99 | 52 | 202 | 53 | 301 | 56 |
| NX | 8 | 4 | 17 | 5 | 25 | n/a |
| **Combination** | | | | | | |
| N0 M0 | 43 | 23 | 84 | 22 | 127 | 22 |
| N+M0 | 31 | 16 | 66 | 18 | 97 | 17 |
| N0 M1 | 39 | 21 | 74 | 20 | 113 | 20 |
| N+ M1 | 68 | 36 | 136 | 36 | 204 | 36 |
| NX M1 | 8 | 4 | 17 | 5 | 25 | 4 |
| **Tumour category** | | | | | | |
| <T3 | 24 | 13 | 36 | 10 | 60 | 11 |
| T3 | 123 | 65 | 249 | 66 | 372 | 69 |
| T4 | 39 | 20 | 68 | 18 | 107 | 20 |
| Tx | 3 | 2 | 24 | 6 | 27 | n/a |
| **Gleason category** | | | | | | |
| <=7 | 35 | 19 | 91 | 25 | 126 | 23 |
| 8 to 10 | 153 | 81 | 276 | 75 | 429 | 76 |
| Unknown | 1 | --- | 10 | --- | 11 | n/a |
| **Previous local therapy** | | | | | | |
| No | 183 | 97 | 350 | 93 | 533 | 94 |
| Yes | 6 | 3 | 27 | 7 | 33 | 6 |
| **WHO performance status** | | | | | | |
| 0 | 149 | 79 | 300 | 80 | 449 | 79 |
| 1 to 2 | 40 | 21 | 77 | 20 | 117 | 21 |
| **Age (years)** | | | | | | |
| <70 | 134 | 71 | 267 | 71 | 401 | 71 |
| 70+ | 55 | 29 | 110 | 29 | 165 | 29 |
| Median (quartiles) | 66 | (62-71) | 66 | (61-70) | 66 | (62-70) |
| Mean (sd) | 66 | (7) | 66 | (7) | 66 | (7) |
| **Use of NSAID or aspirin** | | | | | | |
| No use | 141 | 75 | 280 | 74 | 421 | 74 |
| Uses either | 48 | 25 | 97 | 26 | 145 | 26 |

| Characteristic | SOC+DocP | | SOC+AAP | | Overall | |
|---|---|---|---|---|---|---|
| | | | | | N | % |
| **PSA (ng/ml)** | | | | | | |
| Median (quartiles) | 58 | (29-162) | 55 | (20-194) | 56 | (22-185) |
| Mean (sd) | 193 | (421) | 274 | (631) | 247 | (571) |
| **Ln PSA (ng/ml)** | | | | | | |
| Median (quartiles) | 4.1 | (3.4-5.1) | 4.0 | (3.0-5.3) | 4.0 | (3.1-5.2) |
| Mean (sd) | 4.2 | (1.4) | 4.2 | (1.6) | 4.2 | (1.5) |
| **RT planned** | | | | | | |
| M0, yes | 57 | 77 | 118 | 79 | 175 | 78 |
| M0, no | 17 | 23 | 32 | 21 | 49 | 22 |
| M1, yes | 12 | 10 | 21 | 9 | 33 | 10 |
| M1, no | 103 | 89 | 206 | 91 | 309 | 90 |
| **Hypertension** | | | | | | |
| Yes (still fit for trial) | 64 | 34 | 149 | 40 | 213 | 38 |
| No | 125 | 66 | 227 | 60 | 352 | 62 |
| **Year of randomisation** | | | | | | |
| 2011 | 15 | 8 | 27 | 7 | 42 | 7 |
| 2012 | 138 | 73 | 277 | 73 | 415 | 73 |
| 2013 | 36 | 19 | 73 | 19 | 109 | 19 |

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**Table 2: Hazard ratio for SOC+AAP relative to SOC+DocP from adjusted Cox models**

| Outcome measure | Patient group | Events/Pts SOC+DocP | Events/Pts SOC+AAP | Hazard ratio[3] (95% CI) | p-value | Interaction by metastases p-value |
|---|---|---|---|---|---|---|
| **Failure-free survival[1]** | | | | | | |
| | All | 97/189 | 122/377 | 0·51 (0·39 to 0·67) | <0·001 | |
| | *M0* | *18/74* | *13/150* | *0·34 (0·16 to 0·69)* | *0·003* | |
| | *M1* | *79/115* | *109/227* | *0·56 (0·42 to 0·75)* | *<0·001* | *0·169* |
| **Progression-free survival[1]** | | | | | | |
| | All | 72/189 | 103/377 | 0·65 (0·48 to 0·88) | 0·005 | |
| | *M0* | *10/74* | *9/150* | *0·42 (0·17 to 1·05)* | *0·064* | |
| | *M1* | *62/115* | *94/227* | *0·69 (0·50 to 0·95)* | *0·023* | *0·323* |
| **Metastatic progression-free survival[2]** | | | | | | |
| | All | 71/189 | 118/377 | 0·77 (0·57 to 1·03) | 0·079 | |
| | *M0* | *10/74* | *18/150* | *0·91 (0·42 to 2·01)* | *0·824* | |
| | *M1* | *61/115* | *100/227* | *0·76 (0·55 to 1·04)* | *0·085* | *0·744* |
| **Freedom from symptomatic skeletal events** | | | | | | |
| | All | 36/189 | 63/377 | 0·83 (0·55 to 1·25) | 0·375 | |
| | *M0* | *2/74* | *5/150* | *1·28 (0·24 to 6·67)* | *0·771* | |
| | *M1* | *34/115* | *58/227* | *0·82 (0·53 to 1·25)* | *0·351* | *0·648* |
| **Overall survival** | | | | | | |
| | All | 44/189 | 105/377 | 1·16 (0·82 to 1·65) | 0·404 | |
| | *M0* | *6/74* | *16/150* | *1·51 (0·58 to 3·93)* | *0·395* | |
| | *M1* | *38/115* | *89/227* | *1·13 (0·77 to 1·66)* | *0·528* | *0·691* |

| Outcome measure | Patient group | Events/Pts SOC+Doc | Events/Pts SOC+AAP | Sub-hazard ratio[4] (95% CI) | p-value | Interaction by metastases p-value |
|---|---|---|---|---|---|---|
| **Death from prostate cancer[5]** | | | | | | |
| | All | 40/189 | 86/377 | 1·02 (0·70 to 1·49) | 0·916 | |
| | *M0* | *4/74* | *6/150* | *0·82 (0·24 to 2·81)* | *0·751* | |
| | *M1* | *36/115* | *80/227* | *1·05 (0·71 to 1·56)* | *0·807* | *0·620* |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Death from other causes[6]** | | | | | | |
| | All | 4/189 | 19/377 | 2·33 (0·77 to 6·99) | 0·131 | |
| | *M0* | *2/74* | *10/150* | *3·00 (0·66 to 13·66)* | *0·155* | |
| | *M1* | *2/115* | *9/227* | *1·91 (0·43 to 8·41)* | *0·393* | *0·771* |

[1] Includes death from prostate cancer

[2] Includes death from any cause

[3] From Cox proportional hazards model, adjusted for stratification factors at randomisation (except hospital and choice of hormone therapy) and stratified by time period

[4] From competing risks regression model, adjusted for stratification factors at randomisation (except hospital and choice of hormone therapy) and time period, and treating causes of death other than the focus as a competing event

[5] Cause attributed on central death review; prostate cancer death as event, other cause of death as competing event

[6] Cause attributed on central death review; other causes of death as event, prostate cancer as competing event

**Table 3: Worst adverse event (grade) reported over entire time on trial**

| | **SOC+Doc** (n=189) | **SOC+AAP** (n=377) |
|---|---|---|
| **Safety population** | | |
| Number of patients included in analysis* | **172** | **373** |
| Patients with an adverse event – no. (%) | | |
| Grade 1-5 adverse event | 172 (100) | 370 (99) |
| Grade 3-5 adverse event | 86 (50) | 180 (48) |
| Grade 3-5 adverse events – no. (%) | | |
| Endocrine disorder | 15 (9) | 49 (13) |
| Febrile neutropenia | 29 (17) | 3 (1) |
| Neutropenia (neutrophils) | 22 (13) | 4 (1) |
| General disorder | 18 (10) | 21 (6) |
| *Fatigue* | *7 (4)* | *8 (2)* |
| *Oedema* | *1 (1)* | *2 (1)* |
| Musculoskeletal disorder | 9 (5) | 33 (9) |
| Cardiovascular disorder | 6 (3) | 32 (9) |
| *Hypertension* | *0 (0)* | *12 (3)* |
| *Myocardial Infarction* | *2 (1)* | *4 (1)* |
| *Cardiac dysrhythmia* | *1 (1)* | *5 (1)* |
| Gastrointestinal disorder | 9 (5) | 28 (8) |
| Hepatic disorder | 1 (1) | 32 (9) |
| *Increased AST* | *0 (0)* | *6 (2)* |
| *Increased ALT* | *1 (1)* | *23 (6)* |
| Respiratory disorder | 12 (7) | 11 (3) |
| *Dyspnoea* | *4 (2)* | *1 (1)* |
| Renal disorder | 5 (3) | 20 (5) |
| Lab abnormalities | 9 (5) | 11 (3) |
| *Hypokalaemia* | *0 (0)* | *3 (1)* |

**Table 4: Year of FFS event and death by arm**

| | FFS event | | | | Death | | | |
|---|---|---|---|---|---|---|---|---|
| | SOC+DocP | | SOC+AAP | | SOC+DocP | | SOC+AAP | |
| Year of event | N | % | N | % | N | % | N | % |
| 2012 | 14 | 7% | 25 | 6% | 1 | 1% | 5 | 1% |
| 2013 | 38 | 20% | 43 | 11% | 12 | 6% | 18 | 5% |
| 2014 | 25 | 13% | 33 | 9% | 9 | 5% | 33 | 9% |
| 2015 | 14 | 7% | 11 | 3% | 16 | 8% | 38 | 10% |
| 2016 | 6 | 3% | 10 | 3% | 6 | 3% | 11 | 3% |
| No event | 92 | 49% | 255 | 68% | 145 | 77% | 272 | 72% |

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